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(54) Controlled release hydromorphone composition.

(57) A solid controlled release, oral dosage form, the dosage form comprising a therapeutically effective amount of hydromorphone or a salt thereof in a matrix wherein the dissolution rate in vitro of the dosage form wh n measured by the USP Paddle Method at 100rpm in 900ml aqueous buffer (pH between 1.6 and 7.2) at 37°C is between 12.5% and 42.5% (by weight) hydromorphone released after 1 hour, between 25% and 55% (by weight) hydromorphone released after 2 hours, between 45% and 75% (by weight) hydromorphone released after 4 hours and between 55% and 85% (by weight) hydromorphone released after 6 hours, the in vitro rel ase rate being independent of pH between pH 1.6 and 7.2 and chosen such that the peak plasma level of hydromorphone obtained in vivo occurs between 2 and 4 hours after administration of the dosage form.

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In the present specification, "peak plasma level of hydromorphone obtained in vivo" refers to the maximum mean concentration of hydromorphone found in the plasma of at least six healthy volunteers, when (the volunteers are) subjected to a single dose, pharmacokinetic study.

Preferably the dissolution rate is between 17.5 and 37.5% (by wt) hydromorphone released after 1 hour, between 30 and 50% (by wt) after 2 hours, between 50 and 70% (by wt) after 4 hours and between 60 and 80% (by wt) after 6 hours. Most preferably, the dissolution rate is between 22.5 and 32.5% (by wt) hydromorphone released after 1 hour, between 35 and 45% (by wt) after 2 hours, between 55 and 65% (by wt) after 4 hours and between 65 and 75% (by wt) after 6 hours.

Preferably the peak plasma level of hydromorphone is obtained in vivo between 2.25 and 3.75 hours after administration of the dosage form.

When the hydromorphone is administered as hydromorphone hydrochloride and the method of hydromorphone in plasma analysis is a double antibody radioimmunoassay (as hereinafter described), the peak plasma level of hydromorphone (per ml. of plasma) is preferably between 0.5×10^{-6} and 2.0×10^{-6}, most preferably between 0.5×10^{-6} and 1.5×10^{-6}, of the amount of hydromorphone hydrochloride administered orally.

Thus, if 4mg of hydromorphone hydrochloride is administered, the peak plasma level of hydromorphone is preferably between 2 and 8ngml^{-1}, especially between 2 and 6ngml^{-1}.

When hydromorphone base or a salt other than the hydrochloride is administered, the preferred ratio of drug

hydromorphone at a rate that is independent of pH between 1.6 and 7.2, is that it avoids dose dumping upon oral administration. In other words, the hydromorphone is released evenly throughout the gastrointestinal tract.

The present oral dosage form may be presented as, for example, granules, spheroids or pellets in a capsule or in any other suitable solid form. Preferably, however, the oral dosage form is a tablet.

The present oral dosage form preferably contains between 1 and 100 mg, especially between 2 and 50 mg, most especially between 2 and 40mg, of hydromorphone hydrochloride. Alternatively the dosage form may contain molar equivalent amounts of other hydromorphone salts or of the hydromorphone base.

The present matrix may be any matrix that affords in vitro dissolution rates of hydromorphone within the narrow ranges required and that releases the hydromorphone in a pH - independent manner. Preferably the matrix is a controlled release matrix, although normal release matrices having a coating that controls the release of the drug may be used. Suitable materials for inclusion in a controlled release matrix are

(a) Hydrophilic or hydrophobic polymers, such as gums, cellulose ethers, acrylic resins and protein derived materials. Of these polymers, the cellulose ethers, especially hydroxyalkylcelluloses and carboxyalkylcelluloses, are preferred. The oral dosage form may contain between 1% and 80% (by weight) of at least one hydrophilic or hydrophobic polymer.

aliphatic alcohol in the present oral dosage form will be determined, as above, by the precise rate of hydromorphone release required. It will also depend on whether at least one polyalkylene glycol is present in or absent from the oral dosage form. In the absence of at least one polyalkylene glycol, the oral dosage form preferably contains between 20% and 50%, especially between 25% and 45% (by wt) of the at least one aliphatic alcohol. When at least one polyalkylene glycol is present in the oral dosage form, then the combined weight of the at least one aliphatic alcohol and the atleast one polyalkylene glycol preferably constitutes between 20% and 50%, especially between 25% and 45% (by wt) of the total dosage form.

In the present preferred dosage form, the ratio of the at least one hydroxyalkyl cellulose to the at least one aliphatic alcohol/polyalkylene glycol determines, to a considerable extent, the release rate of the hydromorphone from the formulation. A ratio of the at least one hydroxyalkyl cellulose to the at least one aliphatic alcohol/polyalkylene glycol of between 1:2 and 1:4 is preferred, with a ratio of between 1:3 and 1:4 being particularly preferred.

The at least one polyalkylene glycol may be, for example, polypropylene glycol or, which is preferred, polyethylene glycol. The number average molecular weight of the at least one polyalkylene glycol is preferred between 1000 and 15000 especially between 1500 and 12000.

Another suitable controlled release matrix would comprise an alkylcellulose (especially ethyl cellulose), a C_{12} to C_{36} aliphatic alcohol and, optionally, a polyalkylene glycol.

In addition to the above ingredients, a controlled release

polymer, especially an acrylic polymer, an acrylic copolymer, such as a methacrylic acid-ethyl acrylate copolymer, or ethyl cellulose.

The spheroids are film coated with a material that permits release of the hydromorphone (or salt) at a controlled rate in an aqueous medium. The film coat is chosen so as to achieve, in combination with the spheroids' other ingredients, the in-vitro release rate outlined above (between 12.5% and 42.5% (by wt) release after 1 hour, etc.).

The film coat will generally include a water insoluble material such as

(a) a wax, either alone or in admixture with a fatty alcohol,

(b) shellac or zein,

(c) a water insoluble cellulose, especially ethyl cellulose,

(d) a polymethacrylate, especially Eudragit (Trade Mark).

Preferably, the film coat comprises a mixture of the water insoluble material and a water soluble material. The ratio of water insoluble to water soluble material is determined by, amongst other factors, the release rate required and the solubility characteristics of the materials selected.

The water soluble material may be, for example, polyvinylpyrrolidone or, which is preferred, a water soluble cellulose, especially hydroxypropylmethyl cellulose.

Suitable combinations of water insoluble and water soluble materials for the film coat include shellac and

(b) extruding the blended mixture to give an extrudate,

(c) spheronising the extrudate until spheroids are formed, and

(d) coating the spheroids with a film coat.

Tne present solid, controlled release, oral dosage form and processes for its preparation will now be described by way of example only.

Example 1

Hydromorphone hydrochloride (4.0gm) was wet granulated with lactose monohydrate (167.0gm) and hydroxyethyl cellulose (40.0gm; Natrosol 250 HX, Trade Mark) and the granules were sieved through a 12 mesh screen. The granules were then dried in a Fluid Bed Dryer at 50°C and passed through a 16 mesh screen.

To the warmed hydromorphone containing granules was added molten cetostearyl alcohol (120.0gm) and the whole was mixed thoroughly. The mixture was allowed to cool in the air, regranulated and sieved through a 16 mesh screen.

Purified Talc (6.0gm) and magnesium stearate (3.0gm) were then added and mixed with the granules. The granules were then compressed into 1000 tablets each containing,

	mg/tablet
Hydromorphone Hydrochloride	4.0
Lactose Monohydrate	167.0
Hydroxyethylcellulose	40.0
Cetostearyl alcohol	120.0

	mg/tablet
Hydromorphone Hydrochloride	4.0
Lactose Monohydrate	30.0
Hydroxyethylcellulose	10.0
Methacrylic Acid Copolymer	30.0
Cetostearyl alcohol	30.0

Example 4

Hydromorphone hydrochloride (50g) microcrystalline cellulose (Avicel PH101, 440g) and hydroxypropylmethyl cellulose (Methocel E15, 10g) were dry mixed. Water (350ml) was then added and the mixture was granulated. The granulated mass was extruded through a 1mm cylinder and the extrudate was spheronised. The resultant spheroids were dried at 60°C in a fluid bed drier. The moisture content of the dried spheroids was found to be 4.3% w/w (Karl-Fischer). The dried spheroids were then sieved and the sieve fraction between 1.0mm and 1.4mm was retained.

The spheroids were coated with a film coat, having the formulation given below, to a level of 15% w/w.

Film Coat Formulation

Ethylcellulose N10	4.0% w/v
Hydroxypropylmethylcellulose (Methocel E15)	1.0% w/v
Propylene glycol BP	0.5% w/v
Opaspray K-1-4132	3.0% w/v
Methanol	60.0% v/v
Dichloromethane	to 100.0% v/v

TABLE 2

Time (hr)	wt. % Hydromorphone released
1	26
2	41
3	52
4	60
5	67
6	74
7	79
8	83

In vitro dissolution studies were conducted on tablets prepared as described in Example 3. The dissolution method was the USP Paddle Method described in US Pharmacopoeia XXI (1985). The paddle speed was 100 rpm, the temperature was 37°C and the medium was 900 ml water.

Results are given in Table 3.

Table 3

Time (hr)	wt. % Hydromorphone released
1	35
2	50
3	59
4	66
5	72
6	76
7	80

Analysis of the plasma samples for hydromorphone was performed by a double antibody radioimmunoassay. Plasma was assayed by incubating first with ^{125}Iodohydromorphone and antimorphine antiserum (raised in goats against a 6-hemisuccinyl morphine-BSA conjugate), and subsequently with a solid phase bound antiserum suspension (Sac Cel, anti sheep/goat, Trade Mark). Following the addition of water the samples were centrifuged and the supernatant was removed. The radioactivity in the remaining pellet was counted on a multi-gamma counter for 60 seconds. Results are given in Table 5.

TABLE 5

Time (hr)	Mean Plasma Conc. (ng/ml^{-1})	
	Example 1	Dilaudid
0.50	0.9	9.4
1.0	3.8	8.8
1.50	4.4	8.6
2.0	4.2	7.8
2.5	4.5	7.9
3.0	4.8	6.2
4.0	4.3	3.5
6.0	3.0	3.2
8.0	1.4	1.6
10.0	1.6	1.0
12.0	1.0	0.5
24.0	1.1	0.5

B. A single dose, randomised, comparative, pharmacokinetic study was conducted on 12 subjects employing.

(ii) A normal release hydromorphone hydrochloride tablet (Dilaudid, Trade Mark, a 4mg dose).

Analysis of the plasma samples for hydromorphone was performed and the results are given in Table 7.

TABLE 7

Time (hr)	Mean Plasma Concn. (ng/ml)	
	Example 1	Dilaudid
0	0.12	0.15
0.5	0.57	2.68
1.0	0.67	2.23
1.5	0.74	1.78
2.0	0.75	1.47
2.5	0.72	1.11
3.0	0.69	0.94
3.5	0.65	0.82
4.0	0.59	0.77
5.0	0.71	0.53
6.0	0.59	0.40
8.0	0.40	0.29
10.0	0.49	0.26

CLAIMS

1. A process for the preparation of a solid, controlled release, oral dosage form characterised by incorporating a therapeutically effective amount of hydromorphone or a salt thereof in a matrix wherein the dissolution rate in vitro of the dosage form, when measured by the USP Paddle Method at 100rpm in 900ml aqueous buffer (pH between 1.6 and 7.2) at 37°C is between 12.5% and 42.5% (by weight) hydromorphone released after 1 hour, between 25% and 55% (by weight) hydromorphone released after 2 hours, between 45% and 75% (by weight) hydromorphone released after 4 hours and between 55% and 85% (by weight) hydromorphone released after 6 hours, the in vitro release rate being independent of pH between pH 1.6 and 7.2 and chosen such that the peak plasma level of hydromorphone obtained in vivo occurs between 2 and 4 hours after administration of the dosage form.

2. A process according to claim 1 characterised in that the in vitro dissolution rate is between 17.5% and 37.5% (by weight) hydromorphone released after 1 hour, between 30% and 50% (by weight) hydromorphone released after 2 hours, between 50% and 70% (by weight) hydromorphone released after 4 hours and between 60% and 80%, (by weight) hydromorphone released after 6 hours, preferably between 22.5% and 32.5% (by weight) hydromorphone released after 1 hour, between 35% and 45% (by weight) hydromorphone released after 2 hours, between 55% and 65% (by weight) hydromorphone released after 4 hours and between 65% and 75% (by weight) hydromorphone released after 6 hours.

3. A process according to either claim 1 or claim 2 characterised in that the matrix comprises a controlled release matrix comprising at least one water soluble hydroxyalkyl, preferably

(c) optionally, compressing and shaping the granules

9. A process according to claim 8 characterised in that the at least one water soluble hydroxyalkyl cellulose and the hydromorphone or the salt thereof are wet granulated with water, the weight ratio of the water to the dry weight of the at least one water soluble hydroxyalkyl cellulose being between 1.5 to 1 and 5 to 1, especially between 1.75 to 1 and 3.5 to 1.

10. A process according to claim 1 characterised by blending a mixture comprising hydromorphone or a salt thereof and a non-water soluble spheronising agent, especially microcrystalline cellulose, extruding the blended mixture to give an extrudate, spheronising the extrudate until spheroids are formed and coating the spheroids with a film coat.

10. A dosage form according to any one of claims 1 to 4 in the form of film coated spheroids characterised in that the spheroid matrix comprises a non-water soluble spheronising agent, especially microcrystalline cellulose and, optionally, a water insoluble polymer.

RECEIVING SECTION - FORMALITIES EXAMINATION

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1. Please encode the following marked textcode for the European patent application 87 309 333.0 under Remarks :

☐ Textcode 0401 — The title of the invention has been amended (Guidelines for Examination in the EPO, A-III, 7.3).

☐ Textcode 0402 — The applicant has filed a statement in accordance with Rule 28(4) EPC (issue of a sample only to an expert).
Accesssion Number(s) of the deposit(s) : _____

☒ Textcode 0403 — The application is published incomplete as filed (Art.93(2) EPC). ~~The point in the description or the claim(s) at which the omission obviously occurs has been left blank.~~ First part of claim 4 is obviously missing

☐ Textcode 0404 — Claim(s) _____ is (are) deemed to be abandoned due to non-payment of the claims fee(s) (Rule 31(3) EPC).

☐ Textcode 0406 — The references to the drawing(s) (Fig. _____) are deemed to be deleted (Rule 43 EPC).

☐ Textcode 0410 — For publication purposes, _____ word(s) has (have) been omitted pursuant to Rule 34 EPC at the point(s) marked "*".

☐ Textcode 0414 — For publication purposes, the drawing(s) (Fig. _____) has (have) been omitted pursuant to Rule 34 EPC.

☐ Textcode 0418 — A request for correction (addition) _____
has been filed pursuant to Rule 88 EPC. A decision on the request will be taken during the proceedings before the Examining Division (Guidelines for Examination in the EPO, A-V, 2.2).

☐ Textcode 0420 — Amended claims in accordance with Rule 86(2) EPC.

☐ Textcode 0421 — Amended claims in accordance with Rule 86(2) EPC for the following Contracting State(s) : _____

N.B. : Concerning the textcodes 0420 and 0421 the keyboarding of the amended claims is necessary.

☐ Textcode 0425 — Claim(s) for the following Contracting States : _____

☐ Textcode 0429 — In accordance with the last part of Art. 14(2) EPC the applicant has filed a text with which it is intended to bring the translation into conformity with the original text of the application.

☐ Textcode 0440 — The microorganism(s) has (have) been deposited with _____
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☐ Textcode 0445 — An unreadable (Unreadable) part(s) of the originally filed application documents has (have) been excluded from the publication.

DATE _____ _____ (Signature)

J.H. SCHWARZ 28.03.88

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EUROPEAN SEARCH REPORT

Application Number

EP 87 30 9333

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Y	EP-A-0 156 592 (AMERICAN HOME PRODUCTS CORP.) * Page 5, lines 3-13; page 6, lines 5-10; page 10, lines 7-21, (table 1, test no. 3,5,6); claims *	1-10	A 61 K 31/485 A 61 K 9/22 A 61 K 9/52
Y	US-A-3 965 256 (S.T. LESLIE) * Claims; column 3, lines 37-51; table II; column 8, lines 37-59 *	1-10	
Y	"Rote Liste", 1985, abstract no. 05002; "Dilaudid/dilaudid-atropin/-'schwach'/-'stark'"	1-10	
Y,P	CHEMICAL ABSTRACTS, vol. 108, 1988, pages 326-327, abstract no. 26895u, Columbus, Ohio, US; P.V. PARAB et al.: "Biopharmaceutic parameters of hydromorphone and in vitro evaluation of ita tablet and suppository dosage forms", & PHARM. IND. 1987, 49(9), 951-6	1-10	TECHNICAL FIELDS SEARCHED (Int. Cl.4)
A	US-A-3 492 397 (D. PETERS)	1-10	A 61 K 31/00 A 61 K 9/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	17-03-1988	GERLI P.F.M.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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